Docket No.: 1175

AGNOSE A REQUIRED REGULATION Title: METHOD OF TROPHOBL⁴ VASION

Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848)

WO 98/40747 Phone No.: 612.371.5311

Sheet 1 of 21



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FIGURE 1

```
12-SEP-1993
                                                            PRI
                                             RNA
                                 2574 bp
                    HSTGFB3M
   LOCUS
                    Human mRNA for transforming growth factor-beta 3 (TGF-beta
   DEFINITION
                    3).
                    X14149
   ACCESSION
                    a37095
   NID
                    growth factor; transforming growth factor; transforming
   KEYWORDS
                    growth factor-beta 3.
                    human.
   SOURCE
Homo sapiens
      ORGANISM
                    Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
                    Vertebrata; Eutheria; Primates; Catarrhini; Hominidae;
N
Ō
                    Homo.
                    1 (bases 1 to 2574)
볼
    REFERENCE
                    Chen, E.Y.
U
      AUTHORS
                    Direct Submission
Õ
      TITLE
                    Submitted (23-MAR-1989) Chen E.Y., Genentech Inc., 460 Pt.
      JOURNAL
                    San Bruno Blvd., San Francisco, CA 94080, USA
<u>ļ</u>.
                        (bases 1 to 2574)
TU
    REFERENCE
                    Derynck, R., Lindquist, P.B., Lee, A., Wen, D., Tamm, J.,
ħ.
      AUTHORS
                    Graycar, J.L., Rhee, L., Mason, A.J., Miller, D.A.,
                    Coffey, R.J., Moses, H.L. and Chen, E.Y.
                    A new type of transforming growth factor-beta, TGF-beta 3
      TITLE
                     EMBO J. 7 (12), 3737-3743 (1988)
      JOURNAL
                     89091120
      MEDLINE
                     See <J03241> for alternative sequence of TGF-beta 3.
    COMMENT
                           Location/Qualifiers
    FEATURES
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                                  /db_xref="taxon:9606"
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                                  /cell_line="A172 glioblastoma"
                                  /chromosome="14q24"
                           254..1492
          CDS
                                  /note="TGF-beta 3 (AA 1-412)"
                                  /codon_start=1
                                  /db_xref="PID:g37096"
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```

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BASE COUNT

Ξ

629 a

680 c

666 g

599 t

11

Inventor: CANIGGIA et al.
Docket No.: 1372 38USD1
Title: METH DI DIAGNOSE A REQUIRED REGULATION
OF TROPHO INVASION
Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848)

Phone No.: 612.371.5311

Sheet 2 of 21

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FIGURE 1 (cont'd)

```
ORIGIN
    1 cctgtttaga cacatggaca acaatcccag cgctacaagg cacacagtcc gcttcttcgt
   61 cctcagggtt gccagcgctt cctggaagtc ctgaagctct cgcagtgcag tgagttcatg
  121 cacettettg ccaageetca gtetttggga tetggggagg cegeetggtt tteeteeete
  181 cttctgcacg tctgctgggg tctcttcctc tccaggcctt gccgtccccc tggcctctct
  241 teccagetea cacatgaaga tgcaettgca aagggetetg gtggteetgg eeetgetgaa
  301 ctttgccacg gtcagcctct ctctgtccac ttgcaccacc ttggacttcg gccacatcaa
  361 gaagaagag gtggaagcca ttaggggaca gatcttgagc aagctcaggc tcaccagccc
  421 ccctgagcca acggtgatga cccacgtccc ctatcaggtc ctggcccttt acaacagcac
  481 ccgggagctg ctggaggaga tgcatgggga gagggaggaa ggctgcaccc aggaaaacac
  541 cgagtcggaa tactatgcca aagaaatcca taaattcgac atgatccagg ggctggcgga
  601 gcacaacgaa ctggctgtct gccctaaagg aattacctcc aaggttttcc gcttcaatgt
  661 gtcctcagtg gagaaaaata gaaccaacct attccgagca gaattccggg tcttgcgggt
  721 geccaacee agetetaage ggaatgagea gaggategag etetteeaga teetteggee
  781 agatgagcac attgccaaac agcgctatat cggtggcaag aatctgccca cacggggcac
  841 tgccgagtgg ctgtcctttg atgtcactga cactgtgcgt gagtggctgt tgagaagaga
  901 gtccaactta ggtctagaaa tcagcattca ctgtccatgt cacacctttc agcccaatgg
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 1081 teatetaate eteatgatga tteccecaca eeggetegae aaceegggee aggggggtea
 1141 gaggaagaag cgggctttgg acaccaatta ctgcttccgc aacttggagg agaactgctg
 1201 tgtgcgccc ctctacattg acttccgaca ggatctgggc tggaagtggg tccatgaacc
 1261 taagggetae tatgecaaet tetgeteagg eeettgeeea taeeteegea gtgeagaeae
 1321 aacccacage acggtgctgg gactgtacaa cactctgaac cetgaagcat etgectegee
 1381 ttgctgcgtg ccccaggacc tggagcccct gaccatcctg tactatgttg ggaggacccc
 1441 caaagtggag cageteteca acatggtggt gaagtettgt aaatgtaget gagaceecae
 1501 gtgcgacaga gagaggggag agagaaccac cactgcctga ctgcccgctc ctcgggaaac
 1561 acacaagcaa caaacctcac tgagaggcct ggagcccaca accttcggct ccgggcaaat
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  1681 ggtaaagaaa gtgtgggttt ggttagagga aggctgaact cttcagaaca cacagacttt
  1741 ctgtgacgca gacagagggg atggggatag aggaaaggga tggtaagttg agatgttgtg
  1801 tggcaatggg atttgggcta ccctaaaggg agaaggaagg gcagagaatg gctgggtcag
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  1921 gctctaggga atctggatta tgttatacaa ggcaagcatt tttttttta aagacaggtt
  1981 acgaagacaa agteecagaa ttgtatetea taetgtetgg gattaaggge aaatetatta
  2041 cttttgcaaa ctgtcctcta catcaattaa catcgtgggt cactacaggg agaaaatcca
  2101 ggtcatgcag ttcctggccc atcaactgta ttgggccttt tggatatgct gaacgcagaa
  2161 gaaagggtgg aaatcaaccc tctcctgtct gccctctggg tccctctct cacctctccc
  2221 tegateatat tteeeettgg acaettggtt agaegeette caggteagga tgeacattte
  2281 tggattgtgg ttccatgcag ccttggggca ttatgggtct tcccccactt cccctccaag
  2341 accetgtgtt catttggtgt teetggaage aggtgetaca acatgtgagg cattegggga
  2401 agctgcacat gtgccacaca gtgacttggc cccagacgca tagactgagg tataaagaca
  2461 agtatgaata ttactctcaa aatctttgta taaataaata tttttggggc atcctggatg
  2521 atttcatctt ctggaatatt gtttctagaa cagtaaaagc cttattctaa ggtg
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Inventor: CANIGGIA et al. Docket No.: 1175 USD1

Title: METHOD IAGNOSE A REQUIRED REGULATION

OF TROPHOBL. VASION Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848)

Phone No.: 612.371.5311

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FIGURE 2

```
28-JUN-1995
                                                        PRI
                            3678 bp
                                       mRNA
              HSU22431
  LOCUS
              Human hypoxia-inducible factor 1 alpha (HIF-1 alpha) mRNA, complete
  DEFINITION
              cds.
              U22431
  ACCESSION
              g881345
  NID
E KEYWORDS
  SOURCE
              human.
    ORGANISM
              Homo sapiens
Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
IJ
               Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
               1 (bases 1 to 3678)
Ō
  REFERENCE
               Wang, G.L., Jiang, B.H., Rue, E.A. and Semenza, G.L.
    AUTHORS
Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS
    TITLE
U
               heterodimer regulated by cellular O2 tension
               Proc. Natl. Acad. Sci. U.S.A. 92 (12), 5510-5514 (1995)
D
    JOURNAL
               95296340
    MEDLINE
  REFERENCE
                  (bases 1 to 3678)
               Wang, G.L., Jiang, B.-H., Rue, E.A. and Semenza, G.L.
N
    AUTHORS
               Direct Submission
    TITLE
ħ
               Submitted (09-MAR-1995) Gregg L. Semenza, Center for Medical
     JOURNAL
               Genetics, The Johns Hopkins University School of Medicine, 600 N.
Wolfe St., Baltimore, MD 21287-3914, USA
                        Location/Qualifiers
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                         /cell_type="hepatoblastoma"
                         29..2509
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                         /gene="HIF-1 alpha"
                         29..2509
        CDS
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                         LTDDGDMIYISDNVNKYMGLTQFELTGHSVFDFTHPCDHEEMREMLTHRNGLVKKGKE
                         QNTQRSFFLRMKCTLTSRGRTMNIKSATWKVLHCTGHIHVYDTNSNQPQCGYKKPPMT
                         CLVLICEPIPHPSNIEIPLDSKTFLSRHSLDMKFSYCDERITELMGYEPEELLGRSIY
                         EYYHALDSDHLTKTHHDMFTKGQVTTGQYRMLAKRGGYVWVETQATVIYNTKNSQPQC
                         IVCVNYVVSGIIQHDLIFSLQQTECVLKPVESSDMKMTQLFTKVESEDTSSLFDKLKK
                         EPDALTLLAPAAGDTIISLDFGSNDTETDDQQLEEVPLYNDVMLPSPNEKLQNINLAM
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                         PMDDDFQLRSFDQLSPLESSSASPESASPQSTVTVFQQTQ1QEPTANATTTTATTDEL
                         KTVTKDRMEDIKILIASPSPTHIHKETTSATSSPYRDTQSRTASPNRAGKGVIEQTEK
                         SHPRSPNVLSVALSQRTTVPEEELNPKILALQNAQRKRKMEHDGSLFQAVGIGTLLQQ
                         PDDHAATTSLSWKRVKGCKSSEQNGMEQKTIILIPSDLACRLLGQSMDESGLPQLTSY
                         DCEVNAPIQGSRNLLQGEELLRALDQVN"
                         3678
         polyA site
                          /note="42 A nucleotides"
                                      675 g 1111 t
                              695 c
    BASE COUNT
                   1197 a
```

OF TROPHO INVASION

Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848)

WO 98/40747

Phone No.: 612.371.5311



PCT/CA98/00180

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FIGURE 2 (cont'd)

ORIGIN

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T.J

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1 gtgaagacat cgcggggacc gattcaccat ggagggcgcc ggcggcgcga acgacaagaa
  61 aaagataagt tetgaaegte gaaaagaaaa gtetegagat geageeagat eteggegaag
 121 taaagaatct gaagtttttt atgagettge teateagttg ceaetteeac ataatgtgag
 181 ttcgcatctt gataaggeet etgtgatgag gettaceate agetatttge gtgtgaggaa
 241 acttctggat gctggtgatt tggatattga agatgacatg aaagcacaga tgaattgctt
 301 ttatttgaaa gccttggatg gttttgttat ggttctcaca gatgatggtg acatgattta
 361 catttetgat aatgtgaaca aatacatggg attaactcag tttgaactaa etggacacag
 421 tgtgtttgat tttactcatc catgtgacca tgaggaaatg agagaaatgc ttacacacag
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 541 gaagigtacc ctaactagec gaggaagaac tatgaacata aagtetgeaa catggaaggt
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 661 gtataagaaa ccacctatga cctgcttggt gctgatttgt gaacccattc ctcacccatc
 721 aaatattgaa attootttag atagoaagao tttootoagt ogacacagoo tggatatgaa
 781 attttcttat tgtgatgaaa gaattaccga attgatggga tatgagccag aagaactitt
841 aggccgctca atttatgaat attatcatgc tttggactct gatcatctga ccaaaactca
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1021 accacagige artistatgis igaattacst totsagiget attaticage acgaerigat
1081 tttctccctt caacaaacag aatgtgtcct taaaccggtt gaatcttcag atatgaaaat
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1441 tcaaqaaqtt qcattaaaat tagaaccaaa tccagagtca ctggaacttt cttttaccat
1501 gccccagatt caggatcaga cacctagtcc ttccgatgga agcactagac aaagttcacc
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1681 tactcaggac acagatttag acttggagat gttagctccc tatatcccaa tggatgatga
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1921 tatggaagac attaaaatat tgattgcatc tccatctcct acccacatac ataaagaaac
1981 tactagtgcc acatcatcac catatagaga tactcaaagt cggacagcct caccaaacag
2041 agcaggaaaa ggagtcatag aacagacaga aaaatctcat ccaagaagcc ctaacgtgtt
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2161 agetttgcag aatgeteaga gaaagegaaa aatggaacat gatggtteae ttttteaage
2221 agraggaatt ggaacattat tacagcagcc agacgatcat gcagctacta catcactttc
2281 ttggaaacgt gtaaaaggat gcaaatctag tgaacagaat ggaatggagc aaaagacaat
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2401 attaccacag ctgaccagtt atgattgtga agttaatgct cctatacaag gcagcagaaa
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2581 ctacatctaa ttttagaagc ctggctacaa tactgcacaa acttggttag ttcaattttt
2641 gatcccctt ctacttaatt tacattaatg ctctttttta gtatgttctt taatgctgga
2761 attttaaaaa atgcaccttt ttatttattt atttttggct agggagttta tccctttttc
2821 gaattatttt taagaagatg ccaatataat ttttgtaaga aggcagtaac ctttcatcat
2881 gatcataggc agttgaaaaa tttttacacc tttttttca cattttacat aaataataat
2941 gctttgccag cagtacgtgg tagccacaat tgcacaatat attttcttaa aaaataccag
3001 cagttactca tggaatatat tctgcgttta taaaactagt ttttaagaag aaattttttt
3061 tggcctatga aattgttaaa cctggaacat gacattgtta atcatataat aatgattctt
3121 aaatgetgta tggtttatta tttaaatggg taaageeatt tacataatat agaaagatat
3181 gcatatatet agaaggtatg tggcatttat ttggataaaa tteteaatte agagaaatea
3241 tetgatgttt etatagteae tttgecaget caaaagaaaa caatacceta tgtagttgtg
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3541 aggaatatat agttgtcaca gtaaatatct tgttttttct atgtacattg tacaaatttt
3601 tcattccttt tgctctttgt ggttggatct aacactaact gtattgtttt gttacatcaa
```

SUBSTITUTE SHEET (RULE 26)

3661 ataaacatct tctgtgga

INVASION

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Attorney Name: Kathernie M. Kowalchyk (Reg. No. 36,848) Phone No.: 612.371.5311

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FIGURE 3A

TGFBI TGF82 1. 1113 **B-ACTIN** 6 7 8 gestational age (weeks) IAGNOSE A REQUIRED REGULATION VASION

Attorney Name: Kamerine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311
WO 98/40747
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FIGURE 3B









12 weeks

S weeks (control)

Inventor: CANIGGIA et al.
Docket No.: 11757.381/SD1
Title: METHODS GNOSE A REQUIRED REGULAT.
OF TROPHOBLA:
ASION
Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311
WO 98/40747
Sheet 7 of 21 GNOSE A REQUIRED REGULATION ASION

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FIGURE 4A







Inventor: CANIGGIA et al.
Docket No.: 11757 28 USD1
Title: METHOD: AGNOSE A REQUIRED REGULATION
OF TROPHOBLA VASION
Attomey Name: Katherine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311

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FIGURE 4B

S-B3

AS-B3

AS-B3+B3

200

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Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848) Phone No.: 612.371.5311

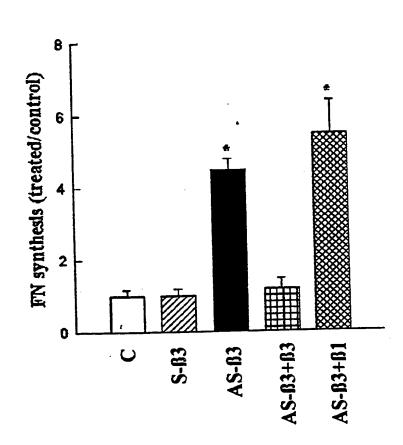
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FIGURE 4C



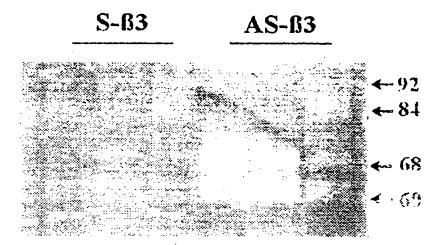
Inventor: CANIGGIA et al.
Docket No.: 11757-28USD1
Title: METHOL PLAGNOSE A REQUIRED REGULATION
OF TROPHOBL VASION
Attorney Name: Kamerine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311

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FIGURE 4D

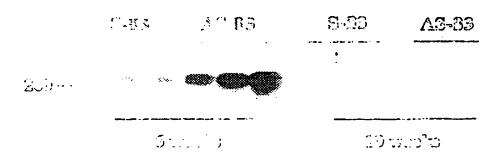


Inventor: CANIGGIA et al.
Docket No.: 11757 231SD1
Title: METHOD3 (AGNOSE A REQUIRED REGULA'
OF TROPHOBLA (ASION
Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311
Sheet 11 of 21 AGNOSE A REQUIRED REGULATION VASION

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FIGURE 4E



Docket No.: 11752 38USD1 Title: METHO DIAGNOSE A REQUIRED REGULATION OF TROPHOB NVASION NVASION

Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848) Phone No.: 612.371.5311

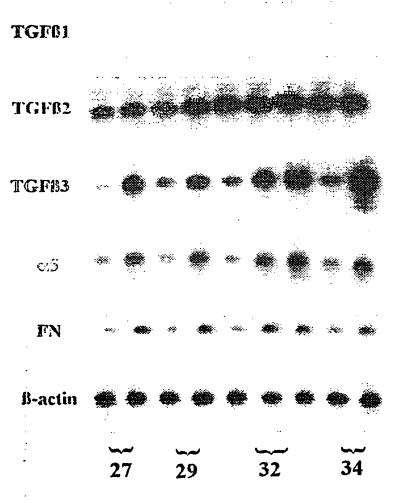
Sheet 12 of 21 WO 98/40747

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FIGURE 5A





gestational age (weeks)

Inventor: CANIGGIA et al.
Docket No.: 11757,38USD1
Title: METHODS AGNOSE A REQUIRED REGULATION
OF TROPHOBLA ASION
Attorney Name: Katherine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311
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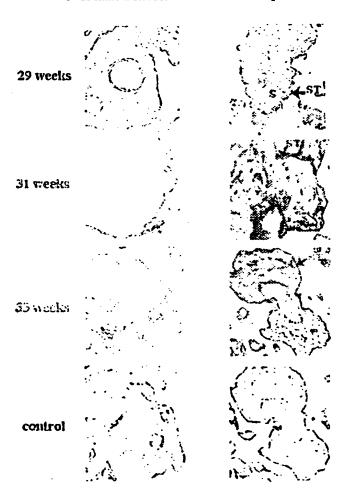
PCT/CA98/00180

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FIGURE 5B

Normal Placenta

Preeclamptic Placenta

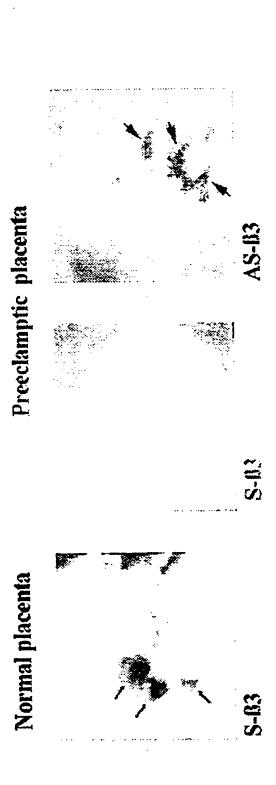


Inventor: CANIGGIA et al.
Docket No.: 11757 38USD1
Title: METHO DIAGNOSE A REQUIRED REGULATION
OF TROPHOL NVASION
Attorney Name: Natherine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311
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Sheet 14 of 21

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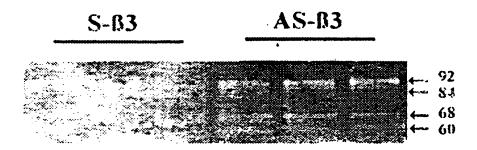


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FIGURE 6B



Inventor: CANIGGIA et al.
Docket No.: 11757.38USD1
Title: METHO DIAGNOSE A REQUIRED REGULATION
OF TROPHOB
Attorney Name: Neuferine M. Kowalchyk (Reg. No. 36,848)
Phone No.: 612.371.5311

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FIGURE 6C

S-B3

AS-B3

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Inventor: CANIGGIA et al.
Docket No.: 11757.38USD1
Title: METHOY DIAGNOSE A REQUIRED REGULATION
OF TROPHOB Attorney Name: Amerine Phone No.: 612.371.5311 merine M. Kowalchyk (Reg. No. 36,848)

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FIGURE 7A

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Title: METI TO DIAGNOSE A REQUIRED REGULATION
OF TROPHO T INVASION
Attorney Name. Katherine M. Kowalchyk (Reg. No. 36,848)

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FIGURE 7B

C PE C PE C PE PE C PE 32

gestational ago (weeks)

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AGNOSE A REQUIRED REGULATION
OF TROPHOBLA
ASION
Attorney Name: Kauserine M. Kowalchyk (Reg. No. 36,848)

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FIGURE 8

20%

TGFB3

HIF

B-ACTIN

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OF TROPH T INVASION
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Phone No.: 612.371.5311
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FIGURE 9

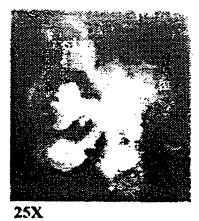
20% O2

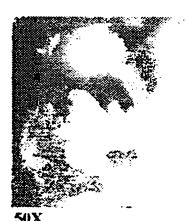




50X

3% O2





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Title: 1 DS TO DIAGNOS .E A REQUIRED REGULATION OF TRU LAST INVASIO N Attorney Name: Katherine M. 1 Kowalchyk (Reg. No. 36,848) Phone No.: 612.371.5311 Sheet 21 of 21

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FIGURE 10

